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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/085,476	02/27/2002	Raffaele De Francesco	IT0002PCA	5843

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EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 08/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/085,476	DE FRANCESCO ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-19* is/are pending in the application.

4a) Of the above claim(s) *8-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 8-19 are still at issue and are present for examination.

Applicants' arguments filed on 5/26/2004, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 8-11 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Rejections - 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 12, 14, 16, 17 and 18 under 35 U.S.C. 103(a) as being unpatentable over Behrens et al. (EMBO 15(1): 12-22, January 1, 1996) is hereby withdrawn based on applicants filing of a translation of applicants priority document, Italy RM95A000343.

The rejection of claims 12, 14, 16, 17 and 18 under 35 U.S.C. 103(a) as being unpatentable over Al et al. (Hepatology 22(4 part 2): 331A, October 1995) is hereby

withdrawn based on applicants filing of a translation of applicants priority document, Italy RM95A000343.

Claims 12, 14, 16, 17 and 18 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Tomei et al. (Journal of Virology 67(7): 4017-4026, July 1993). The rejection was stated in the previous office action and repeated below.

Tomei et al. teach that the Hepatitis C virus (HCV) is considered to be the major etiologic agent of post-transfusion non-A, non-B hepatitis and that the NS5 region of the HCV polyprotein is cleaved into two smaller products of 47 and 65 kDa. Tomei et al. also teach that the NS5B region contains a GDD sequence characteristic of RNA-dependent RNA polymerases (RdRp) and they suggest that this protein may act as a viral RNA replicase during HCV-specific RNA synthesis and also function in the replication of the viral genome, acting as a component of the replication complex involved in the reaction (page 4024, column 1, paragraph 5). Tomei et al. further teach DNA constructs and transient expression of the HCV genome and characterize the post-translational processing of the HCV transcript, and specifically transcribe and translate NS5B, described by SEQ ID NO: 1. (see page 4020, Figure 1 and also Figure 3A).

One of ordinary skill in the art at the time of the filing of the invention would have been motivated to incubate together the HCV NS5B protein, ribonucleotide substrates and a RNA template under conditions suitable to produce RNA-dependent RNA polymerase, wherein said incubation takes place *in vitro* in order to further characterize

the function and role of the protein(s) encoded by the NS5B ORF. The expectation of success comes from the high degree of skill in the art with respect to protein expression, as demonstrated by Tomei et al. in their expression of the HCV cDNA encoding the entire polyprotein using a vaccinia virus T7 expression system. One of ordinary skill at the time of invention would have been motivated to produce the NS5B protein both by the independent transcription and translation of the NS5B as well as by the proteolytic processing of the NS2-NS3-NS4-NS5 polyprotein to determine if the proteolytic processing event affects the activity of the NS5B protein product. One would have been further motivated to vary the RNA templates and primers in the incubation mixture to characterize the specific mechanism of action of any RNA-dependent RNA polymerase activity. The motivation for the addition of ribonucleotide substrates and a RNA template comes from the suggestion by Tomei et al. that the NS5B encodes a RNA-dependent RNA polymerase. The reasonable expectation of success comes from the teaching of Tomei et al. that while the nonstructural region of the HCV genome has not been characterized in detail, it is thought to be processed in a manner similar to that of flaviviruses and pestiviruses and the hydropathy profile of HCV polyprotein is similar to that of the flavivirus polyprotein as well as the suggestion that the NS5B ORF encoded protein is a RNA-dependent RNA polymerase. One of ordinary skill in the art at the time of filing of the application would have been further motivated to incubate together the HCV NS5B protein, ribonucleotide substrates and a RNA template under conditions suitable to produce RNA-dependent RNA polymerase activity, wherein said incubation takes place *in vitro* in the presence of potential target molecules which may

inhibit the action of the NS5B protein as a means of identifying potential therapeutics to be used against the NS5B protein and HCV. The motivation for why one of skill in the art would be interested in the function of the NS5B ORF is because as one of only a few HCV encoded nonstructural proteins the protein(s) encoded by the NS5B ORF is a prime target for the development of therapeutics against HCV. A reasonable expectation of success comes from the high degree of knowledge in the art with respect to protein expression and the identification of inhibitors of said proteins activity, as discussed above.

In response to this rejection applicants have not amended the claims but rather traverse the rejection as it appears to the previous claims.

Applicants submit that Tomei et al. fails to provide a reasonable expectation of success that NS5B can be used in an *in vitro* assay for identifying a HCV RNA-dependent RNA polymerase inhibitor because Tomei et al. does not provide data demonstrating that NS5B provides RNA-dependent RNA polymerase activity. Applicants further submit that one of skill in the art would have no motivation to perform an assay measuring RNA-dependent RNA polymerase activity from NS5B *in vitro* to assay for a HCV polymerase inhibitor. Finally, applicants submit that there is uncertainity as to whetherNS5B provides RNA-dependent RNA polymerase activity and whether, if it encodes a polymerase, it can be used in an *in vitro* assay to identify inhibitors.

Applicants complete argument is acknowledged, however found non-persuasive for the reasons stated previously and below.

With respect to applicants assertion that Tomei et al. fails to provide a reasonable expectation of success that NS5B can be used in an *in vitro* assay for identifying a HCV RNA-dependent RNA polymerase inhibitor, because Tomei et al. does not provide data demonstrating that NS5B provides RNA-dependent RNA polymerase activity, data demonstrating with certainty that the NS5B is a RNA-dependent RNA polymerase is unnecessary.

As previously stated, the reasonable expectation of that the NS5B is a RNA-dependent RNA polymerase is based on that Tomei et al. also teach that the NS5B region contains a GDD sequence characteristic of RNA-dependent RNA polymerases (RdRp) and they suggest that this protein may act as a viral RNA replicase during HCV-specific RNA synthesis and also function in the replication of the viral genome, acting as a component of the replication complex involved in the reaction (page 4024, column 1, paragraph 5). Certainty that the NS5B protein is a RNA-dependent RNA polymerase is unnecessary, merely the high probability, as suggested by Tomei et al. Further given that the NS5B is most likely a RNA-dependent RNA polymerase, their would be a reasonable expectation of success that it could be used in an assay to identify inhibitors of HCV RNA-dependent RNA polymerase inhibitors. The expectation of success of such is based on in addition to that taught by Tomei et al. the high level of skill in the art with respect to the recombinant expression of proteins, their identification and the identification of inhibitors of the identified activity (i.e. RNA-dependent RNA polymerase activity).

With respect to applicants assertion that there is no motivation to perform an assay measuring RNA-dependent RNA polymerase activity from NS5B *in vitro* to assay for a HCV polymerase inhibitor as previously stated, one of ordinary skill in the art at the time of the filing of the invention would have been motivated to incubate together the HCV NS5B protein, ribonucleotide substrates and a RNA template under conditions suitable to produce RNA-dependent RNA polymerase, wherein said incubation takes place *in vitro* in order to further characterize the function and role of the protein(s) encoded by the NS5B ORF, because as previously stated, Tomei et al. teach that the Hepatitis C virus (HCV) is considered to be the major etiologic agent of post-transfusion non-A, non-B hepatitis and that the NS5 region of the HCV polyprotein is cleaved into two smaller products of 47 and 65 kDa, one of which, the NS5B, region contains a GDD sequence characteristic of RNA-dependent RNA polymerases (RdRp) and they suggest that this protein may act as a viral RNA replicase during HCV-specific RNA synthesis and also function in the replication of the viral genome, acting as a component of the replication complex involved in the reaction (page 4024, column 1, paragraph 5). Thus as RNA synthesis and viral replication is an important and necessary step of the HCV life-cycle, inhibitors of this step are a logical target for therapeutic intervention. Thus the motivation exists to use the NS5B protein, the presumed HCV RNA-dependent RNA polymerase, as a target for their identification.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

As previously stated, claims 12, 14, 16, 17 and 18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-15 of U.S. Patent No. 6,383,768. An obvious type double patenting rejection is appropriate where conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g.., *In re* Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re* Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re* Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 8-15 of U.S. Patent No. 6,383,768 drawn to a method for measuring the ability of a compound to affect hepatitis C virus (HCV) NS5B activity comprising: (a) incubating in vitro a composition comprising HCV NS5B, ribonucleotide substrates, an RNA template, and said compound, under conditions suitable to produce NS5B RNA-dependent RNA polymerase activity, wherein said NS5B is provided to said

composition from a preparation wherein said NS5B is the only HCV protein present and (b) measuring the ability of said compound to affect said NS5B RNA-dependent RNA polymerase activity anticipates claims 12, 14, 16, 17 and 18 of the instant application.

Applicants acknowledgement of this rejection is noted.

The rejection of claims 13, 15 and 19 under 35 U.S.C. 101 as claiming the same invention as that of claims 8, 15 and 11 of prior U.S. Patent No. 6,383,768 is hereby withdrawn based on applicants traversal, however, these claims are included in the above obviousness-type double patenting as being unpatentable over claims 8-15 of U.S. Patent No. 6,383,768 for the reasons previously stated for claims 12, 14, 16, 17 and 18.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Remarks

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (571) 272-0930. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh
8/4/2004